

## INTERVENTIONAL CARDIOLOGY AND SURGERY

# Type II diabetes does not prevent the recruitment of collateral vessels and the normal reduction of myocardial ischaemia on repeated balloon inflations during angioplasty

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**Objective:** To test whether type II diabetes prevents the recruitment of collaterals and the normal reduction of myocardial ischaemia on repeated balloon inflations during coronary angioplasty.

**Methods:** Two groups of patients were studied. A *collateral circulation group* consisted of 56 patients, 18 diabetic and 38 non-diabetic. All underwent a minimum of three balloon inflations. A pressure guide wire was used for the measurement of coronary wedge pressure (mm Hg). The angioplasty protocol was repeated in another group of 57 patients (*myocardial ischaemia group*) using both surface and intracoronary ECGs to assess myocardial ischaemia.

**Results:** In diabetic patients, mean (SD) coronary wedge pressure was 35 (12) mm Hg during the first balloon inflation, 39 (15) mm Hg during the second ( $p < 0.05$  v first inflation), and 42 (17) mm Hg during the third ( $p < 0.05$  v first inflation); in non-diabetic patients the respective values were 36 (16), 37 (16), and 37 (16) mm Hg ( $F = 4.73$ ,  $p = 0.01$ ). The ratio of coronary wedge pressure to mean arterial pressure in diabetic patients in the three balloon inflations was 0.33 (0.11), 0.36 (0.13), and 0.39 (0.15), respectively ( $p < 0.05$  v the first inflation); and in non-diabetic patients it was 0.33 (0.15), 0.34 (0.15), and 0.35 (0.15) ( $F = 1.92$ ,  $p = 0.15$ ). In the diabetic group the response was independent of the type of treatment. No difference between diabetic and non-diabetic patients was observed in the normal reduction of myocardial ischaemia on repeated balloon inflations.

**Conclusions:** Type II diabetes does not prevent the recruitment of collateral vessels and the normal reduction of myocardial ischaemia on repeated balloon inflations during coronary angioplasty in single vessel disease, regardless of the type of antidiabetic treatment.

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Collaterals develop in the advanced stages of coronary atherosclerosis.<sup>1</sup> Although not all aspects of the mechanisms underlying the development of coronary collaterals are fully understood, the pivotal role of myocardial ischaemia is well established.<sup>2–3</sup> However, there is much variation in collateral development in patients with ischaemic heart disease. The factors responsible for this variation are not well known.<sup>4</sup> Histological studies have documented the thin walled capillary-like morphology of "mature" collateral vessels in the early stages of their development.<sup>4</sup> In later stages of development collaterals grow actively, as demonstrated by mitotic activity in the endothelial and smooth muscle cells.<sup>5</sup> Patients with coronary artery disease who have diabetes mellitus have a less favourable outcome than those without diabetes, including a three- to fourfold increase in mortality risk.<sup>6–8</sup> Moreover, diabetic patients with non-fatal myocardial infarction have a more complicated course, including more frequent postinfarction angina, infarction extension, and congestive heart failure.<sup>9</sup> The reason for this is not clear.<sup>10</sup> However, diffuse endothelial dysfunction is thought to be one of the main elements in the process.<sup>11</sup> Endothelial cells are important in the development and maturation of coronary collateral vessels.<sup>12–13</sup>

It has been shown that in the course of coronary angioplasty the severity of myocardial ischaemia during balloon inflation decreases with subsequent inflations, confirming an adaptive response of the myocardium.<sup>14</sup> In principle, two components—preconditioning and opening of coronary collateral channels—could contribute to this tolerance of myocardial ischaemia. We know that most of the oral hypoglycaemic agents (sulfonylureas) reduce ischaemic

preconditioning,<sup>15</sup> and the diabetic myocardium is also inherently less responsive to preconditioning.<sup>16</sup> Accordingly, our aim in this study was to assess the role of type II diabetes in the recruitment of coronary collaterals and in the normal reduction of myocardial ischaemia on repeated balloon inflations during angioplasty. Coronary angioplasty is a useful model for the study of the clinical, systemic, metabolic, and coronary haemodynamic responses to controlled coronary arterial occlusion.<sup>14–17</sup>

## METHODS

### Patients

The study was approved by the hospital ethics committee, and all patients gave their written informed consent. The study had two parts, studying two different groups of patients: in the *collateral circulation group* we examined the effect of type II diabetes on the recruitment of collateral circulation on repeated balloon inflations during angioplasty; in the *myocardial ischaemia group* we studied the role of type II diabetes in the normal reduction of myocardial ischaemia in the same clinical setting.

We studied patients undergoing elective coronary angioplasty for an isolated obstructive lesion in the proximal one third of a coronary artery. All lesions caused an internal diameter reduction of 50–90%, as determined by quantitative

**Abbreviations:**  $P_a$ , aortic pressure;  $P_{wv}$ , coronary wedge pressure;  $Q_{cr}$ , collateral flow;  $Q_{Nv}$ , maximum myocardial perfusion

**Table 1** Clinical features of the patients studied

	Collateral circulation group		Myocardial ischaemia group	
	Diabetic (n=18)	Non-diabetic (n=38)	Diabetic (n=18)	Non-diabetic (n=39)
Age (years)	57 (130)	58 (11)	61 (9)	58 (11)
Sex (male/female)	14/4	32/6	16/2	35/4
Baseline heart rate (beats/min)	68 (8)	70 (9)	69 (10)	69 (9)
Baseline MBP (mm Hg)	105 (12)	103 (16)	102 (14)	103 (14)
Smokers	10	18	9	19
Treatment of diabetes				
Diet	3	–	9	–
Oral antidiabetic agents	10	–	7	–
Metformin	5	–	3	–
Sulfonylurea	7	–	6	–
Insulin	5	–	2	–
Total cholesterol (mmol/l)	5.54 (1.11)	5.72 (1.24)	6.19 (1.32)	5.67 (1.22)
LV ejection fraction (%)	57 (4)	58 (4)	61 (7)	59 (6)
Dilated coronary artery				
Left anterior descending	11	20	12	22
Right coronary	5	13	5	12
Left circumflex	2	5	1	5
Stenosis severity before angioplasty (%)	75 (9)	77 (7)	76 (14)	74 (12)
Balloon size (mm)	2.5 (0.3)	2.6 (0.3)	2.6 (0.3)	2.7 (0.4)
Atmospheres applied	12 (2)	12 (3)	13 (2)	13 (2)

Values are n or mean (SD).

LV, left ventricular; MBP, mean blood pressure.

coronary arteriography. Patients with stenoses of more than 90% were excluded, in order to avoid “preinflation ischaemia” caused by obstruction from the guide wire across the lesion, which would prolong the ischaemic time of the first inflation compared with the second.<sup>17</sup>

All patients fulfilled the following entry criteria: they had a history of chronic stable angina pectoris for three months or more, and they had a normal left ventricular ejection fraction.

Exclusion criteria were: unstable angina; conduction defects or baseline ST segment abnormalities on the ECG; history or ECG evidence of previous myocardial infarction; angiographic evidence of collateral circulation; evidence of left ventricular hypertrophy on the ECG; history of systemic hypertension.

### Angioplasty protocol

All drugs except for aspirin were discontinued 12 hours before the procedure. No glucose/insulin infusions were given during the procedure. All patients were studied after an overnight fast and were not premedicated with sedatives. A standard Seldinger technique was used. Heparin (5000 IU intra-arterially) was given as a bolus at the beginning of the procedure and during angioplasty to maintain an activated clotting time of 250–300 seconds.

No other drugs were given until the end of the third balloon inflation. After the balloon was positioned across the lesion, three balloon inflations of 120 seconds’ duration were given with the same inflation pressure. A minimum period of five minutes was allowed for reperfusion between the balloon inflations. Measurements were recorded at the end of each of the three inflations, just before deflation. After the third balloon inflation sequence, the experimental part of the procedure was completed and coronary angioplasty was then concluded in accordance with standard clinical criteria.

### Collateral circulation group

The collateral circulation group included 56 patients (table 1), 18 with type II diabetes and 38 without diabetes. The other clinical characteristics of these two subgroups were the same. More than half (56%) of the diabetic patients were on oral antidiabetic agents (usually sulfonylureas).

The WaveWire, a 0.014 inch (0.36 mm) diameter, high fidelity pressure recording guide wire (Cardiometrics, Mountain View, California, USA), using advanced piezoresistive

technology, was calibrated externally and then introduced into the haemostatic valve, advanced to the distal tip of the guide catheter, and used to verify that equal pressures were recorded by both the guiding catheter and the pressure wire. The WaveWire was subsequently advanced into the distal part of the diseased artery. During balloon inflation this wire gives the coronary wedge pressure ( $P_w$ ). After the balloon was positioned across the lesion, three balloon inflations of 120 seconds’ duration were performed.

### Collateral measurement

By combining  $P_w$ , obtained from the WaveWire, with simultaneously recorded aortic pressure ( $P_a$ ), obtained from the guiding catheter, and central venous pressure at maximum arterial vasodilatation, a quantitative index of collateral flow can be calculated.<sup>18</sup> This index, called fractional collateral blood flow, expresses actual collateral flow ( $Q_c$ ) as a ratio to normal maximum myocardial perfusion ( $Q_N$ ).

The collateral circulation can be estimated according to the formula<sup>18</sup>:

$$Q_c/Q_N = P_w/P_a$$

### Myocardial ischaemia group

The myocardial ischaemia group included consecutive patients, 18 with type II diabetes and 39 without diabetes (table 1). The clinical characteristics of these two subgroups were otherwise the same. Half the diabetic patients were on antidiabetic diet and 19% were on oral antidiabetic drug treatment (mainly with sulfonylureas).

### Assessment of myocardial ischaemia

Lead V5 of the ECG was connected to the coronary guide wire.<sup>19</sup> The intracoronary ECG and two surface ECG leads chosen to reflect likely areas of ischaemia during angioplasty were recorded at a paper speed of 25 mm/s throughout the study (Mingograf, Siemens, Germany). Intracoronary and surface ECG recordings were made after 120 seconds during the first three balloon inflations. Patients without intracoronary ECG ST elevation were excluded from the study.

The ECGs were analysed by a physician (NC) who had no knowledge of the study protocol. ST segment elevation was measured 80 ms after the J point. The severity of myocardial ischaemia was expressed in two ways: first in terms of the ST

**Table 2** The variables during the three balloon inflations in the patients in the collateral circulation group

Variable	Subgroup (n)	1st BI	2nd BI	3rd BI	F value	p Value
Heart rate (beats/min)	Diabetic (18)	67 (9)	67 (7)	67 (7)	0.45	0.64
	Non-diabetic (38)	73 (11)	72 (11)	72 (11)		
MAP (mm Hg)	Diabetic (18)	105 (13)	110 (13)	108 (12)	2.48	0.08
	Non-diabetic (38)	110 (20)	111 (17)	108 (17)		
RPP ( $\times 10^3$ )	Diabetic (18)	7.0 (1.4)	7.4 (1.4)	7.2 (1.3)	2.34	0.10
	Non-diabetic (38)	8.1 (2.0)	8.0 (1.8)	7.8 (1.7)		
CWP (mm Hg)	Diabetic (18)	35 (12)	39 (15)*	42 (17)*	4.73	0.01
	Non-diabetic (38)	36 (16)	37 (16)	37 (16)		
CWP/MAP	Diabetic (18)	0.33 (0.11)	0.36 (0.13)	0.39 (0.15)*	1.92	0.15
	Non-diabetic (38)	0.33 (0.15)	0.34 (0.15)	0.35 (0.15)		

Values are mean (SD).

\* $p < 0.05$  v first balloon inflation.

BI, balloon inflation; CWP, mean coronary wedge pressure; MAP, mean arterial pressure; RPP, rate-pressure product (heart rate  $\times$  mean blood pressure).

elevation from baseline on the intracoronary ECG; second in terms of the ST segment elevation on the surface ECG lead with the largest ST shift (both expressed in mV).

### Statistical analysis

All data are expressed as mean (SD). Analysis of variance with repeated measures was used for statistical analysis, followed by Tukey's honestly significant difference test for post hoc comparisons. Linear regression analysis using the least squares difference was used to examine possible correlations between changes in surface and intracoronary ECG and plasma cholesterol concentrations. A probability value of  $p < 0.05$  was considered significant.

## RESULTS

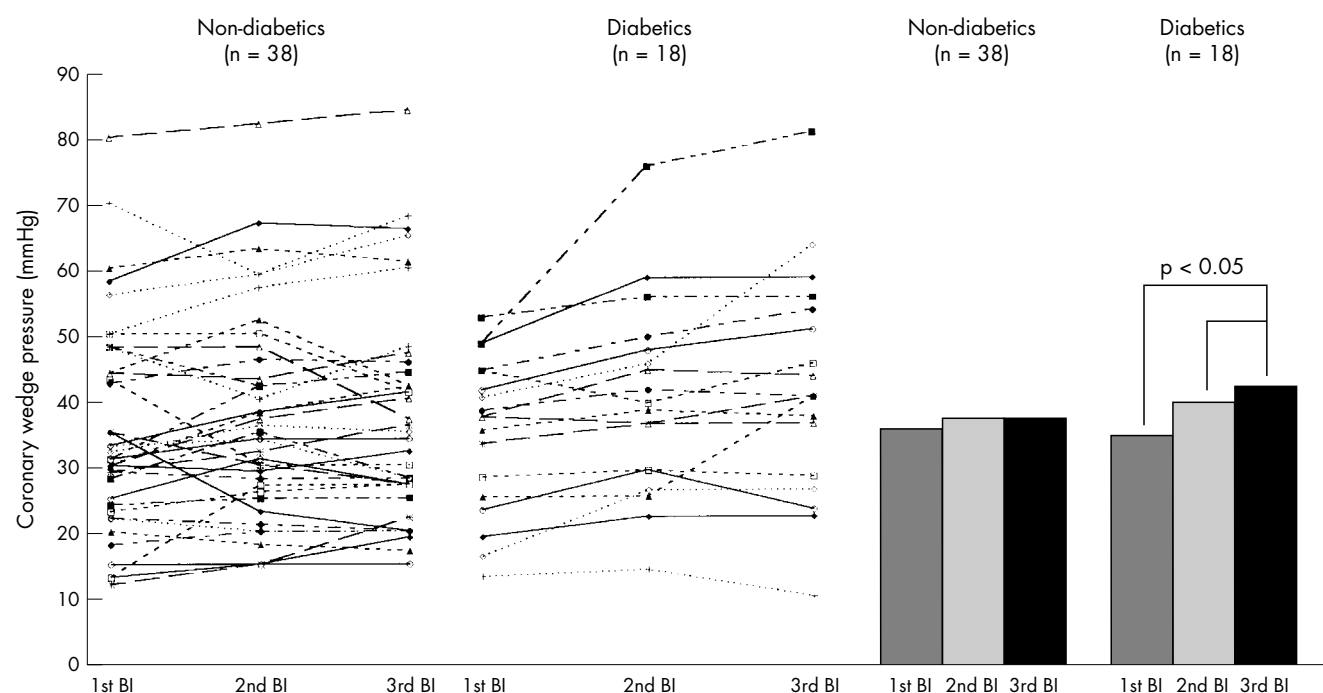
No complications caused by the study protocol were recorded.

### Collateral circulation group

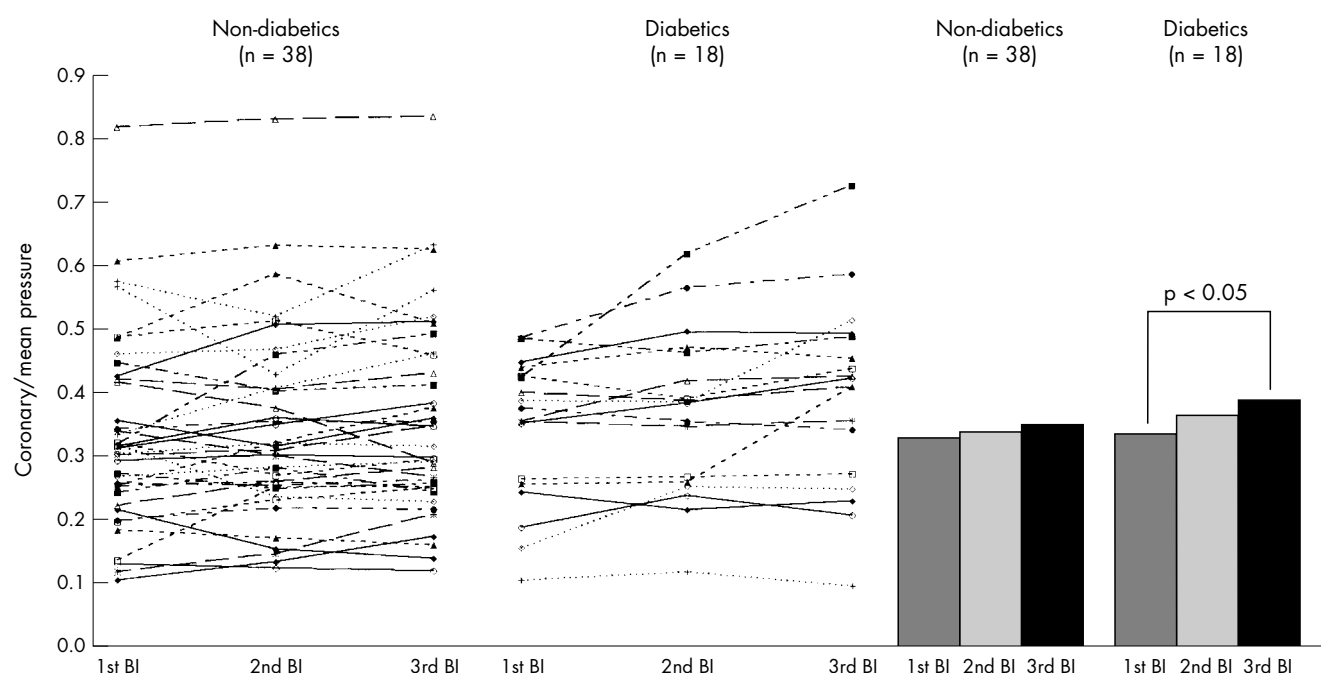
Heart rate was the same in the two subgroups (diabetic and non-diabetic) during the three balloon inflations. Mean arterial pressure and double product in the diabetic patients showed a tendency to increase, whereas in the non-diabetic patients they showed a tendency to decrease (table 2).

Coronary wedge pressure in the diabetic patients increased by 20% from the first to the third balloon inflation ( $p < 0.05$ ), while in the non-diabetic patients it increased by 3% (NS) ( $F = 4.73$ ,  $p = 0.01$ ) (table 2, fig 1). This change was almost the same for each type of antidiabetic treatment: +22% in patients on diet, +21% in patients on oral antidiabetic drug treatment, and +22% in patients on insulin ( $F = 0.31$ , NS).

The coronary wedge/mean arterial pressure in the diabetic patients increased from the first to the third balloon inflation by 18% ( $p < 0.05$ ), whereas in the non-diabetic subgroup it increased by only 3% (NS) ( $F = 1.92$ ,  $p = 0.15$ ) (table 2, fig 2).



**Figure 1** Mean individual values of coronary wedge (CWP) pressure at the end of the first, second, and third balloon inflations (BI) in the two subgroups (diabetic and non-diabetic) of the coronary circulation group. In the diabetic patients CWP increased progressively between the three balloon inflations. In contrast, in the non-diabetic patients CWP did not increase significantly.



**Figure 2** Mean individual values of coronary wedge pressure (CWP)/mean arterial pressure at the end of the first, second, and third balloon inflations (BI) in the two subgroups (diabetic and non-diabetic) in the coronary collateral group. In the diabetic patients, the CWP/mean arterial pressure increased significantly from the first to the third inflation. In contrast, in the non-diabetic patients this change was not significant.

This change was similar for each type of antidiabetic treatment: +15% in patients on diet, +19% in patients on oral antidiabetic drug treatment, and +13% in patients on insulin ( $F = 0.49$ , NS).

### Myocardial ischaemia group

Heart rate, mean arterial pressure, and double product were the same in the two subgroups (diabetic and non-diabetic) during the three balloon inflations (table 3).

In the diabetic patients, intracoronary ST segment elevation decreased from the first to the third balloon inflation by 43% ( $p < 0.05$ ) and in the non-diabetic patients by 29% ( $p < 0.05$ ) ( $F = 0.39$ , NS) (table 3). In the diabetic patients the change from the first to the third balloon inflation did not differ significantly according to the type of antidiabetic treatment: -40% in patients on diet, -40% in patients on oral antidiabetic drug treatment, -19% in patients on insulin ( $F = 0.69$ , NS).

Surface ST segment shift decreased in the diabetic patients between the first and the third balloon inflation by 32% (NS) and in the non-diabetic patients by 47% ( $p < 0.05$ ) ( $F = 0.06$ , NS) (table 3). In the diabetic patients the change from the first to the third balloon inflation did not differ significantly according to the type of treatment: -22% in patients on diet, -42% in patients on oral antidiabetic drug treatment, -55% in patients on insulin ( $F = 0.04$ , NS).

There was a significant correlation ( $r = 0.54$ ,  $p < 0.0001$ ) between the decrease of surface and intracoronary ST segment shift from the first to the third balloon inflation. A correlation was also found ( $r = -0.41$ ,  $p = 0.02$ ) between the surface ST segment shift from the first to the third balloon inflation and the plasma cholesterol concentrations.

### DISCUSSION

Our results suggest that type II diabetes does not prevent the recruitment of collateral vessels or the normal reduction in

**Table 3** The variables during the three balloon inflations in the patients in the myocardial ischaemia group

Variable	Subgroup (n)	1st BI	2nd BI	3rd BI	F value	p Value
Heart rate (beats/min)	Diabetic (18)	74 (9)	73 (10)	72 (8)	0.05	0.9
	Non-diabetic (39)	72 (10)	71 (10)	69 (9)		
MBP (mm Hg)	Diabetic (18)	111 (16)	107 (16)	110 (24)	0.45	0.6
	Non-diabetic (39)	114 (23)	111 (14)	109 (15)		
RPP ( $\times 10^3$ )	Diabetic (18)	8.2 (1.7)	7.9 (1.8)	8.0 (2.6)	0.49	0.6
	Non-diabetic (39)	8.3 (2.4)	7.9 (1.4)	7.6 (1.4)		
Intracoronary ST elevation (mV)	Diabetic (18)	1.03 (0.53)	0.79 (0.42)	0.59 (0.41)*	0.39	0.7
	Non-diabetic (39)	1.31 (0.76)	1.06 (0.67)*	0.93 (0.71)*		
Surface ST elevation (mV)†	Diabetic (9)	0.25 (0.20)	0.19 (0.21)	0.17 (0.22)	0.05	0.9
	Non-diabetic (29)	0.19 (0.14)	0.13 (0.10)*	0.10 (0.12)*		

Values are mean (SD).

\* $p < 0.05$  v first balloon inflation.

†The number of the patients with surface ST elevation was reduced owing to the fact that patients were excluded from the analysis of this variable when no surface ST elevation was present.

BI, balloon inflation; MAP, mean arterial pressure; RPP, rate-pressure product (heart rate  $\times$  mean blood pressure).

myocardial ischaemia on repeated balloon inflations during coronary angioplasty.

### Diabetes mellitus and collateral circulation

Heinle *et al* showed that diabetes mellitus is not associated with decreased collaterals.<sup>20</sup> On the other hand, Abaci *et al*,<sup>21</sup> in a retrospective study, suggested that coronary collateral vessel development is reduced in patients with diabetes mellitus. For the estimation of collateral circulation Abaci *et al* used the angiographic method,<sup>22</sup> which is subjective. These studies had several limitations. Firstly, angiographically visible collaterals represent only a fraction of the total number of collateral vessels, because collaterals are angiographically demonstrable only when they reach 100  $\mu\text{m}$  in diameter. Angiography may not detect most of the collateral vessels situated intramurally. Thus the collaterals visualised by angiography may not quantify the collateral circulation accurately. In our study we used the fractional collateral blood flow, which is an objective index of collateral circulation and has been validated in animals and humans.<sup>18</sup> Secondly, in both the above mentioned studies, which were retrospective and non-randomised, there could have been effects on the collateral circulation from various drugs given during angiography, whereas in our study no drug treatment was given during the procedure or for at least 12 hours before. Thirdly, in the study by Abaci *et al* the diabetic patients had more severe (multivessel) coronary artery disease than the non-diabetic patients,<sup>21</sup> a factor that interferes with the angiographic determination of coronary collaterals, whereas our patients had single vessel disease and the collateral circulation was evaluated under the same conditions for all the patients—that is, total occlusion of the diseased artery.

Our results show that the collateral circulation is not diminished but enhanced during repeated balloon inflations in diabetic patients, in comparison with non-diabetic patients. Under normal conditions blood flow depends on the pressure gradient between the interconnecting arterial networks; thus there is only minimal net forward flow, and small amounts of flow may oscillate within the network.<sup>23</sup> When there is significant arterial narrowing, blood flow increases through these networks. Following a sudden arterial occlusion, such as in angioplasty, a steep pressure gradient develops along the shortest path within the interconnecting network, and this causes an increase in blood flow velocity. It has been shown in a previous study<sup>14</sup> that collateral blood flow has a tendency to increase with repeated balloon inflations.

The reason why diabetic patients develop better collateral recruitment is not clear. Possible mechanisms for this could include, firstly, the existence of more collateral neoangiogenesis in diabetes (there are reports showing that diabetes mellitus does not inhibit the formation of collateral vessels in the heart<sup>24</sup>), and secondly, the secretion of higher concentrations of vasoactive substances in diabetes. In non-obese diabetic mice it has been shown that diabetes impairs the endogenous neovascularisation of ischaemic tissues and that the impairment of new blood vessel formation results from a reduced expression of vascular endothelial growth factor (VEGF).<sup>25</sup> Supplementation by intramuscular adeno-VEGF gene transfer restores neovascularisation in a mouse model of diabetes mellitus.<sup>25</sup> These observations contrast with studies on angiogenesis in the context of diabetic retinopathy. In that situation, high concentrations of VEGF have been identified in the ocular fluids of diabetic patients.<sup>26</sup> The mechanisms whereby VEGF expression could differ from one tissue to another are not known. It is possible that the transcription or post-transcriptional regulation of VEGF could vary depending on the cell type (skeletal myocytes versus retinal cells). Unfortunately, in the present study cardiac VEGF expression was not evaluated.

### Diabetes mellitus and normal reduction of myocardial ischaemia on repeated balloon inflation

Sulfonylureas inhibit ischaemic preconditioning,<sup>15</sup> and the diabetic myocardium per se is resistant to preconditioning.<sup>16</sup> Sulfonylureas may have different effects on myocardial preconditioning during ischaemia, given that some new compounds such as glimeperide have been shown not to inhibit preconditioning.<sup>27</sup> However, none of our patients was taking one of these new drugs. It might be expected that diabetes mellitus would cause greater myocardial ischaemia and inhibition of the normal reduction of myocardial ischaemia on repeated balloon inflations during angioplasty. Our data (table 3) show equal myocardial ischaemia in diabetic and non-diabetic patients during the first balloon inflation. Diabetic patients on oral antidiabetic drugs did not have more significant myocardial ischaemia or inhibition of the normal reduction of myocardial ischaemia on repeated balloon inflations compared with those on other treatments (although the numbers in some of these subgroups were very small). This is in accordance with recent data showing that the failure to precondition the diabetic heart reflects dysfunction of mitochondrial  $\text{K}_{\text{ATP}}$  channels and not necessarily the chronic administration of sulfonylureas.<sup>16</sup> A possible explanation for the absence of greater myocardial ischaemia or inhibition of the normal reduction in myocardial ischaemia during repeated balloon inflations in diabetic patients is that the inhibition of ischaemic preconditioning is counteracted by the increase in recruitment of coronary collaterals in these patients.

### Conclusions

Type II diabetes does not prevent the recruitment of coronary collaterals and the normal reduction of myocardial ischaemia on repeated balloon inflations during coronary angioplasty in patients with single vessel disease, regardless of the type of antidiabetic treatment.

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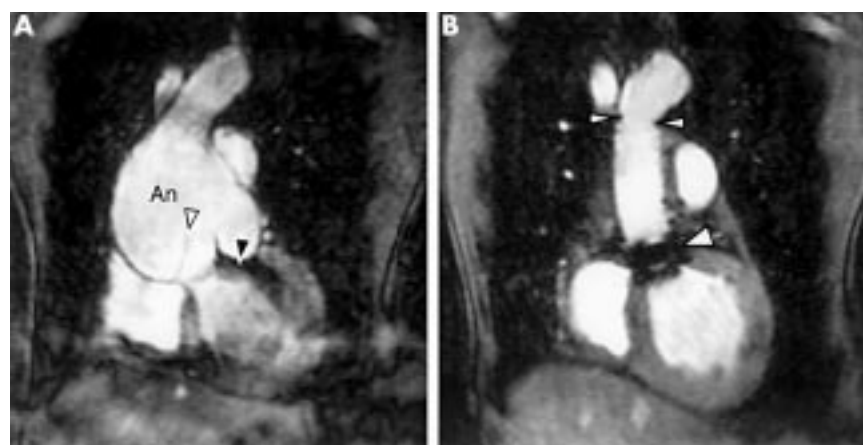
## IMAGES IN CARDIOLOGY.....

### Asymptomatic aortic dissection in Marfan syndrome

A 26 year old English teacher with Marfan syndrome had been lost to follow up for two years in which time his aortic root had dissected and increased in diameter from 4.4 cm to 8.5 cm, without symptoms.

He had previously had mitral valve repair for valve prolapse, and there was a strong family history of early sudden death. He had attended annual follow up from the age of 14 years until two years ago when he went to teach abroad. On previous visits his systolic blood pressure had never exceeded 110 mm Hg and aortic root measurements by echocardiography had been steady at 4.4 cm. He was not on  $\beta$  blockers because of asthma. He re-attended after returning to the country.

Although he was asymptomatic, on clinical examination signs of severe aortic regurgitation were found. He was admitted and magnetic resonance imaging (MRI) was performed. It showed (panel A) a flask shaped aneurysm (An) confined to the aortic root and lower ascending aorta with a maximum diameter of 8.5 cm, and a dissection flap (white arrow). The turbulent aortic regurgitant jet (black arrow head) represents severe aortic incompetence. The patient underwent emergency aortic root replacement with a St Jude valved conduit, and made a



full recovery. The postoperative MRI (panel B) showed good surgical result, the signal void from the metal ring of the St Jude valve (large arrow head) and the distal suture line of the conduit (paired small arrow heads).

This case illustrates that aortic dissection in Marfan syndrome can be asymptomatic and vigilant follow up is essential for such patients.

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